Biophysical Journal Volume 104 February 2013 746–747

New and Notable

A Tale of Two Ions and their Membrane Interactions: Clearly the Same or Clearly Different?

Thomas B. Woolf*

Department of Physiology, Johns Hopkins University, School of Medicine, Baltimore, Maryland

The article by Knecht and Klasczyk in this issue of *Biophysical Journal* determines similar binding affinities for Na and Cl interacting with POPC membranes (1). Their joint experimental and computational refinement shows the power of combining data from multiple experimental and computational approaches. Understanding the molecular nature of these interactions is important for membrane protein function, bilayer dynamics, and cellular biophysics. Early work with membrane electrostatics showed the importance of the placement of charge and suggested that dielectric screening could be a functional component of membrane behavior (2,3). From that beginning point, detailed molecular dynamics simulations have begun to illustrate that the behavior of cations and anions may or may not vary within different regions of the membrane bilayer (4,5). This, in turn, could lead to significant changes in bilayer shape and function as the concentration and types of anions or cations are varied (6).

The work of Knecht and Klasczyk (1), combining experimental work on electrophoresis and calorimetry with all-atom molecular dynamics calculations, suggests that force fields and the sampling of lipid and ionic interactions are still not sufficiently evolved to fully predict and interpret experimental measurements. The long-time and large-scale averages determined by experiment are not fully predicted and rationalized by the computations. Furthermore, as the authors point out, the simulations are in disagreement with each other, depending on force field, boundary conditions, and simulation size and time. Teasing out whether the issues are only force-field dependent, or also a function of sampling or system size, is a difficult issue that needs to be resolved.

Further creating intrigue for our evolving understanding of the effects of charge on membrane function is the experimental findings that the size of the anion/cation matters. For example, the Hofmeister series has been found to be important as an organizing principle for the effects of anions in membrane behavior (7–9). If the electrostatic function alone were the dominant factor, then the type of anion would be much less important. So, finding out how and why size does play a role in the membrane behavior remains an intriguing area for research. This may also tie back into a need for improved force fields that can better predict the experimental results. It will be important to understand if the Hofmeister effects are related to binding, kinetics, or nonspecific screening effects.

Gaining a molecular understanding of ion effects, even in water, has proven to be challenging from a molecular viewpoint (10). Efforts to improve the current generation of force fields, supporting induced polarization, are encouraging and suggest that convergence in simulation results may be improved by the next generation of force fields (11). These have yet to be fully applied to membrane simulations and the comparison of the results to earlier simulations and experiments will be interesting.

For membrane protein function and the cellular biophysics of networks, these types of salt effects may also drive meaningful change. For example, if ion channels and ionic transport mechanisms are both directly and indirectly impacted by the distribution and types of charge, then this may play a role in their interconnections through the bilayer and may, in turn, change their functional specificity and kinetics. This implies that the behavior of membrane proteins and their associated connections to peptides, other proteins, and the bilayer environment, may be tied together with the seemingly straightforward, but still difficult, problem of how salt distributes in a membrane system.

Thus, the article by Knecht and Klasczyk should be read as part of a continuing dialog on the interpretation of thermodynamic measurements at the molecular level and the role of simple systems in providing insights into the larger issues of cellular biophysics, membrane transport, and ionic interactions. It may presage the development of new insights into the physical properties of bilayers that update a view of dielectric screening based on boundary layers and nonspecific interactions with proteins and membrane headgroups.

REFERENCES

1. Knecht, V., and B. Klasczyk. 2013. Specific binding of chloride ions to lipid vesicles and implications at molecular scale. *Biophys. J.* 104:818–824.
2. Parsegian, A. 1969. Energy of an ion crossing a low dielectric membrane: solutions to four relevant electrostatic problems. *Nature.* 221:844–846.
3. Honig, B. H., W. L. Hubbell, and R. F. Flewelling. 1986. Electrostatic interactions in membranes and proteins. *Annu. Rev. Biophys. Biophys. Chem.* 15:163–193.
4. Berkowitz, M. L., and R. Vácha. 2012. Aqueous solutions at the interface with phospholipid bilayers. *Acc. Chem. Res.* 45:74–82.
5. Valley, C. C., J. D. Perlmutter, …, J. N. Sachs. 2011. NaCl interactions with phosphatidylcholine bilayers do not alter membrane structure but induce long-range ordering of ions and water. *J. Membr. Biol.* 244:35–42.
6. Khandelia, H., and O. G. Mouritsen. 2009. Lipid gymnastics: evidence of complete acyl chain reversal in oxidized phospholipids from molecular simulations. *Biophys. J.* 96:2734–2743.

Submitted December 21, 2012, and accepted for publication January 10, 2013.

*Correspondence: twoolf@jhu.edu

Editor: Scott Feller.

0006-3495/13/02/0746/2 $2.00

http://dx.doi.org/10.1016/j.bpj.2013.01.010

7. Aroti, A., E. Leontidis, …, T. Zemb. 2007. Effects of monovalent anions of the Hofmeister series on DPPC lipid bilayers. Part I. Swelling and in-plane equations of state. *Biophys. J.* 93:1580–1590.

8. Clarke, R. J., and C. Lüpfert. 1999. Influence of anions and cations on the dipole potential of phosphatidylcholine vesicles: a basis for the Hofmeister effect. *Biophys. J.* 76:2614–2624.

9. Sachs, J. N., and T. B. Woolf. 2003. Understanding the Hofmeister effect in interactions between chaotropic anions and lipid bilayers: molecular dynamics simulations. *J. Am. Chem. Soc.* 125:8742–8743.

10. Grossfield, A., P. Y. Ren, and J. W. Ponder. 2003. Ion solvation thermodynamics from simulation with a polarizable force field. *J. Am. Chem. Soc.* 125:15671–15682.

11. Lamoureux, G., and B. Roux. 2006. Absolute hydration free energy scale for alkali and halide ions established from simulations with a polarizable force field. *J. Phys. Chem. B.* 110:3308–3322.